REMARKS

As an initial matter, applicants and their counsel wish to express their appreciation to Examiners Lundgren and Schultz for the courtesy of the interview held on October 16, 2007. While no agreement was reached regarding the pending claims (all were discussed), the discussion which took place among those present (Messrs. Lundgren and Schultz, Dr. Thomas W. Leonard, Chief Scientific Officer of the assignee of the present application, and the undersigned) was quite helpful in understanding how the teachings of the references cited in the outstanding Office Action have been applied to the pending claims and how potential amendments may delineate the claimed invention more clearly.

Reconsideration of the allowability of the pending claims in view of the foregoing amendments, the following remarks, and the Declaration of James Swarbrick, D.Sc., Ph.D., filed herewith, is requested respectfully.

Status of the Claims

Claims 178, 182-188, 196, 198, 202-206, 208-214, 222-228, 236, 238-240, 244-246, 250, 251, and 253-256 have been amended, and the support for such amendments may be found throughout the specification. In view of the number of claims that have been amended, the applicants will defer the presentation of a lengthy citation chart as support for all of the claims is readily found upon review of the specification. Should the Examiner have any concern regarding the support for any particular claim amendment, the applicants request respectfully that the Examiner contact the undersigned so that such concern may be addressed.

No new claims have been added, claims 1-177, 179-181, 199-201, and 215-221 have been canceled, and claims 189-195, 197, 207, 229-235, 237, 241-243, 247-249, 252, and 257 have been withdrawn from consideration as being drawn to a non-elected invention.

The Office Action mailed March 18, 2005, required the applicants to make a species election for the drug and the medium chain fatty acid salt. According to that Office Action:

> Both the search and the examination of a large number of claims drawn to a large number of different Drugs, medium chain (C6-C20) fatty acids and/or fatty acid derivatives which differ in chemical structure, function, properties and which are capable of different methods of making and use is unduly burdensome .... (Office Action at 3)

In response to this requirement, the applicants elected low molecular weight heparin (LMWH) as the drug, and sodium caprate as the medium chain fatty acid salt. In view of these elections, the applicants consider claims which recite heparin, anti-coagulants, polysaccharides, and hydrophilic or macromolecular drugs as readable on the elected invention. Accordingly, the applicants consider claims 178, 182-188, 196, 198, 202-206, 208-214, 222-228, 236, 238-240, 244-246, 250, 251, and 253-256 as readable on the elected invention and are presented for further examination.

Remarks Concerning Rejections in Office Action

Standards for Anticipation Under 35 U.S.C. § 102

A rejection under 35 U.S.C. § 102 is proper only if each and every element of a claim is found in a single prior art reference, arranged as in the claim. MPEP § 2131; *Brown v. 3M*, 265 F.3d 1349, 60 USPQ2d 1375 (Fed. Cir. 2001). The corollary entailed by this principle is that where a cited reference does ***not*** contain each and every element of the claim, it ***cannot*** support a rejection under 35 U.S.C. § 102.

As to whether each and every element may be found in a single reference, the Federal Circuit has said that an anticipatory reference "must describe the claimed invention ***with sufficient precision and detail*** to establish that the subject matter existed in the prior art." *Verve, LLC. V. Crane Cams, Inc.*, 311 F.3d 1116, 65 USPQ2d 1051 (Fed. Cir. 2002) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it.")) (emphasis added).

General Remarks Regarding Oral Dosage Formulations

It is generally known that a pharmaceutically active compound must be present in solution in the gastrointestinal tract (GIT) before it can pass through the epithelial cells lining the GIT wall (by any of a variety of mechanisms) and into the patient's bloodstream. *See* Declaration of James Swarbrick, P.Sc., Ph.D. ("Swarbrick Declaration") at ¶ 3. In the pharmaceutical industry, drug formulations are usually developed initially as liquid formulations as these forms are the simplest to manufacture and test. *Id.* at ¶ 4. However, in the development of a particular active ingredient, there is a general desire in the industry to progress from liquid formulations to solids (e.g. powder, capsule, granulate, tablet, etc.). *Id.* The desire to progress to solid forms can be traced to a number of advantages common to solid formulations that cannot be readily obtained by using liquids. *Id.* at ¶ 5. These advantages are many and include the following:

- Greater stability of active compounds in the solid state.
- Longer shelf life of solids over liquid formulations.
- Solid forms more tamper-evident than liquids.
- Greater dosing accuracy in solid dosage forms.
- Lower manufacturing costs for solid dosage forms
- Lower shipping, packaging, and storage costs for solid forms.

Id.

Various different solid formulations exist including tablets, capsules, granulates, and powders. Swarbrick Declaration at ¶ 6. In the pharmaceutical industry, there is a general preference for tablets over capsules, and a preference for capsules over liquid formulations. *Id.* Both tablets and capsules are preferred over liquid formulations as they each provide convenient unit dosage forms, and tablets are preferred over capsules as they are easier and less expensive to manufacture. *Id.* Although tablets are the drug formulation of choice, the formation of tablets requires the careful manipulation of a variety of different parameters. *Id.* at ¶ 7.

The typical procedure for forming a pharmaceutical tablet, described in broad terms, involves:

(1) forming a compressible powder or granulate blend; and

(2) compressing an amount of the powder or granulate blend in a tablet press to form a tablet.

Swarbrick Declaration at ¶ 7. If desired, the tablet may then be coated with a coating to modify and/or delay the release of the tablet components from the tablet. *Id.* Powder or granulate blends that are to be compressed into tablets may be formed by "dry" methods, such as by dry blending powders or granules of the tablet components, or by "wet" methods, such as by forming a paste, slurry, or solution of the tablet components which is then spray dried or granulated to form a free flowing powder or granulate. *Id.*

One important factor in the formation of tablets is that the powder or granulate blends that are to be compressed into tablets are dry, preferably free-flowing, materials. Swarbrick Declaration at ¶ 8. If the material is not dry, or if it is a waxy or a paste material, it does not flow freely into the tablet press and is difficult to compact into tablet. *Id.* Where such material can be compacted, it is difficult to form a tablet that is properly released from the tablet press and that has the requisite structural integrity. *Id.*

In some circumstances, it may be desirable to apply a coating to a tablet in order to isolate the tablet components from the stomach. . Swarbrick Declaration at ¶ 17. Such coated tablets are commonly referred to as delayed release or enteric tablets. *Id.* Delayed release tablets may be desirable where the active component in the tablet can be degraded by acidic environments, or where any of the components of the tablet may be stomach irritants. *Id.* In these situations, the coating serves to isolate the tablet components from the stomach environment to avoid the undesirable stomach irritation or loss of tablet efficacy. *Id.*

A delayed release coating may be formed from material that is a solid at room temperature and that is melted, applied in a molten state, and which then cools to form the coating. Swarbrick Declaration at ¶ 18. Alternatively, the coating material may be applied as a solution or suspension which is then dried to form the coating. *Id.* In either case, one of the steps in the coating process (the coating step in the first case, and the drying step in the second case) is performed at elevated temperatures. *Id.* As a result, the

components of the tablet must be chemically and structurally stable at these elevated temperatures. *Id.* Accordingly, while a tablet may be formed containing a significant amount of a component having a melting point below 50°C, it would not be possible to apply a delayed release coating to such a tablet without substantial risk of losing tablet integrity due to the melting of one or more of the components. *Id.*

Bachynsky

Claims 178-181, 183, and 240 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bachynsky et al., Irish Patent No. (11) 63119, and Bachynsky et al., U.S. Patent No. 5,190,748 (collectively, "Bachynsky"). This rejection is respectfully traversed.

According to the Examiner, Bachynsky teaches a process for providing a blend of a ceftriaxone and a salt of a medium chain fatty acid having a carbon chain length of from 6 to 20 carbon atoms, with optional constituents Laureth-12 and Witepsol™ H15. The Examiner further characterizes the blend of Bachynsky, as well as each constituent thereof, as solids at room temperature, and that the blend of Bachynsky is capable of being formed into oral dosage forms, including enterically coated dosage forms, in which sodium caprylate serves as an enhancer.

As discussed at the Interview of October 16, 2007, Bachynsky is directed ***exclusively*** to the use of dual-component absorption enhancers. Specifically, the dual-component absorption enhancers of Bachynsky comprise:

1. A first component:
   an ether of a C6-C18 alcohol and a polyethylene glycol, in combination with
2. A second component selected from among:
   (a) polyoxyethylene glycol C6-C18 glyceride esters;
   (b) C6 to C18 carboxylic acids or salts thereof; and
   (c) esters of two or more C6-C18 carboxylic acids, glycerol and a polyoxyethylene glycol.

See Bachynsky (US) at col. 2, lines 2-18. Bachynsky identifies Laureth-12 as a preferred material for the first component, and as preferred or exemplary materials for each of the three alternative second components Bachynsky identifies Labrasol, sodium caprate, and Aconno Con, respectively. *See* Bachynsky (US) at col. 5, lines 22-31; col. 6, lines 17-20, 35-42; col. 7, lines 7-14.

In view of the materials Bachynsky describes, the absorption enhancers that Bachynsky discloses would be considered microemulsions, a term generally understood to refer to stable liquid systems of water, oil, and an amphiphile. Swarbrick Declaration at ¶ 10; s*ee also*, Danielsson and Lindman, "The definition of Microemulsion", Colloids and Surfaces, 3 (1981), 391-392 (Elsevier Scientific Publishing Co.) (a microemulsion is "a system of water, oil, and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution."). To one of ordinary skill in the art, the teachings of Bachynsky are thus viewed properly within the context of developments in the field of microemulsion systems and as such systems are applied to absorption enhancement.

All of the drug formulations disclosed in Bachynsky include the polyoxyethylene glycol lauryl ether Laureth-12. Swarbrick Declaration at ¶ 10. Laureth-12 has a melting point just above room temperature and is a soft waxy compound at room temperature. *Id.* Many of the formulations in Bachynsky also contain "Witepsol H15" which is typically used as a suppository base. *Id.* Notably, even the oral formulations described in Bachynsky include Witepsol H15 (for example the compositions on page 14, lines 15-19). *Id.* Witepsol H15 also has a melting point just above room temperature and is also a soft waxy compound at room temperature. *Id.*

All of the oral formulations in Bachynsky contain a considerable amount of low-melting waxy compounds (e.g., Laureth-12 and Witepsol H15). Swarbrick Declaration at ¶ 11. For example the compositions described in the table on page 14 of Bachynsky contain between 47% and 62% (weight percent) waxy compounds. *Id.* These waxy compounds make it very difficult to compress the compositions into tablets, and it would therefore not be practical, and therefore not commercially viable, to form tablets by simply compressing the compositions described in Bachynsky. *Id.*

In general, the dosage forms described in Bachynsky are capsules that are filled with the mixture of a drug and a two-component enhancer system. Swarbrick Declaration at ¶ 9. The only disclosure of non-capsule forms is on page 7, lines 15-19, where Bachynsky mentions the possibility of forming tablets and proposes absorbing a liquid formulation of the mixture of the drug and the two-component enhancer system onto a carrier followed by compression to form a tablet. *Id.* The proposal in Bachynsky to absorb a liquid formulation onto a carrier followed by compression to form a tablet (page 7, lines 15-19) is not actually a viable proposal for the compositions described in Bachynsky. *Id.* at ¶ 12. Inasmuch as the compositions all contain significant amounts of soft, low-melting materials (Laureth-12 and/or Witepsol H15), a very large amount of carrier (such as silica) would be required to provide a composition dry enough to be successfully pressed into tablets. *Id.* The use of such large amounts of carrier material would result in either a tablet suitable for oral administration but too small to contain a unit dose, or a unit dose tablet too large to be orally administered. *Id.* Moreover, despite the suggestion in Bachynsky, the applicants are unaware of any actual use in the industry of a tablet preparation process in which soft, low-melting materials in liquid form are absorbed onto a solid carrier which is then compressed to form a tablet. *Id.* at ¶ 13.

While Bachynsky recites several medium chain fatty acid salts as suitable for use, such references are entirely within, and limited to, a framework in which such materials are one of three alternatives for the second component of a two-component absorption enhancing microemulsion system. All of the compositions and dosage forms of Bachynsky that recite a medium chain fatty acid salt do so ***only*** in combination with a second component (such as Laureth-12) that, together, forms a microemulsion and, in that manner, functions as an absorption enhancer. Swarbrick Declaration at ¶ 10.

In sum, Bachynsky neither teaches nor suggests a compressible composition or a solid oral dosage form containing an absorption enhancer in which the absorption enhancer is:

1. in particulate form;
2. in a compressible blend admixed with a drug in particulate form;
3. a sodium salt of a medium chain fatty acid; and

4. a single-component enhancer – i.e., not combined with, for example, an ether of a C6-C18 alcohol and a polyethylene glycol, and not part of a two-component system, for example, a microemulsion.

In the absence of such teachings, Bachynsky fails to disclose the claimed invention with sufficient precision and detail as to establish that the subject matter existed in the prior art. As a result, Bachynsky does not meet the disclosure standards required for anticipation and, therefore, cannot serve as the basis for a rejection under 35 U.S.C. § 102(b). Accordingly, the applicants request respectfully that the rejections based on Bachynsky be withdrawn.

Watts

Claims 178, 182-184, 186, 188, 198, 202-204, 209, 211-214, 222-224, 226, 228, 238-240, 244-246, 250, 251, and 253-256 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Watts et al., WO 97/05903 ("Watts"). This rejection is respectfully traversed.

As noted at the Interview of October 16, 2007, Watts discloses unambiguously the use of a ***two-component*** absorption promoter as follows.

> The present invention therefore provides a drug delivery composition for colonic delivery comprising a polar drug, an absorption promoter which (a) comprises a mixture of a fatty acid having 6 to 16 carbon atoms or a salt thereof *and a dispersing agent* or (b) comprises a mixture of mono/diglycerides of medium chain fatty acids *and a dispersing agent* and means adapted to release the polar drug and absorption promoter in the colon.

Watts at page 5, lines 10-16 (emphasis supplied). Both of the Watts embodiments describe the absorption promoter as a ***two-component mixture*** in which one component must be a dispersing agent while the other may be either: (1) a medium chain fatty acid or salt; or (2) a mixture of mono/diglycerides of medium chain fatty acids. While additional details are provided as to particular fatty acids and salts, mono and diglycerides, and dispersing agents that are suitable in the practice of the Watts invention, the scope of Watts' invention extends ***only*** to the use of two-component absorption promoters. All of

the embodiments which employ a medium chain fatty acid or salt thereof in the absorption promoter ***must also contain*** a dispersing agent as a second component of the absorption promoter.

As with Bachynsky, Watts describes two-component absorption promoters that would be considered microemulsions. Swarbrick Declaration at ¶ 14. Accordingly, to one of ordinary skill in the art, the teachings of Watts, like those of Bachynsky, are thus viewed properly within the context of developments in the field of microemulsion systems as such systems are applied to the promotion of absorption.

According to the Examiner, however, Watts discloses a drug delivery composition comprising a drug such as LMWH and an absorption promoter such as capric acid. *See* Office Action at 5. While the Examiner does acknowledge the presence of the non-ionic surfactant Labrasol, it is referred to not as the preferred material for the dispersant component of the absorption promoter but as an "auxiliary excipient." Further, by being described in Watts as a "dispersing agent," this material is somehow considered to be something ***other*** than an essential component of the absorption promoter. *Id.* Viewed, however, in light of the teachings of Watts as a whole, and in particular within the microemulsion context, the central role of the dispersing agent as an essential component of the ***two-part absorption promoter*** becomes evident.

Watts also mentions, in generalized terms, formulating the compositions as tablets or pellets (page 9, lines 14-17) using "known tablet constituents and methods." Swarbrick Declaration at ¶ 14. The compositions in Watts are "liquid or semi-solid" depending on the length of the fatty acid carbon chain (page 8, line 21-23), and those presented in the examples of Watts are all either liquids or pastes. *Id.* In order to form tablets from any of the compositions described in Watts, it would be necessary to alter such compositions substantially in order to form a compressible powder or granulate blend. *Id.* at ¶ 16. Any suggestion to absorb the liquids of Watts onto a carrier material (such as proposed in Bachynsky) suffers from the same problems noted above with respect to Bachynsky, i.e., the need for significant quantities of carrier material. *Id.* Moreover, despite the suggestion in Watts to use to "known tablet constituents and methods," the applicants are not aware of constituents or methods that could be used to make commercially viable, orally administrable tablets from the compositions of Watts.

As previously noted, Watts discloses a composition of sodium insulin and capric acid in a comparative example (Example 3) in order to demonstrate the inferior effect of capric acid as the only enhancer compared to the synergistic effect realized by their two-component microemulsions. It is important to note that this disclosure is limited ***only*** to the capric acid, and does not include any disclosure of any medium chain fatty acid salt, by itself, in combination with a drug. As demonstrated in the samples presented in the interview, sodium caprate is a flowable, compressible, water-soluble powder at room temperature, whereas capric acid is a congealed, incompressible, and water-insoluble mass. As shown in the table below, there are very substantial differences in the physical properties of capric acid as compared with its sodium salt. These differences carry over into the resultant properties of mixtures of each with an active ingredient, and these differences are significant.

	Sodium caprate	Capric acid
Molecular Formula	$C_{10}H_{19}O_2Na$	$C_{10}H_{20}O_2$
Melting Point	240°C	31°C
Description	White to cream coloured powder	White crystals
Solubility	Soluble in water	Immiscible in water

With regard to the teachings of Watts, a composition of sodium insulin and capric acid, as described in Example 3 of Watts, was produced in accordance with the teachings of Watts. Swarbrick Declaration at ¶ 15. As noted above, capric acid has a melting point of 31°C and is immiscible in water. Because its melting point is so close to room temperature, it is not possible to form a homogeneous particulate mixture of capric acid with an active ingredient having a sufficiently small particle size to be suitable for tableting or dry encapsulation. The very act of mechanically mixing capric acid with an active ingredient will impart sufficient energy to the capric acid to cause it to melt. To avoid this, Watts teaches one to melt capric acid by heat and to add the sodium insulin to the resulting liquid. The final composition, at room temperature, is a semi-solid mass of capric acid and sodium insulin in the form of a paste. *Id.* In such form, it does not flow freely into a tablet press and is difficult to compact into tablet. *Id.* at ¶ 8. Where such

material can be compacted, it is difficult to form a tablet that is properly released from the tablet press and that has the requisite structural integrity. *Id.*

By contrast, sodium caprate has a very high melting point so that a homogeneous particulate mixture of sodium caprate and an active ingredient that has sufficiently suitable characteristics for tableting or dry encapsulation may be readily formed. Due to its high solublity in water, tablets manufactured with this a sodium caprate mixture will dissolve very quickly and will have a drug load that can be readily absorbed. As a result, the comparative example in Watts of a mixture of capric acid and sodium insulin is a disclosure quite unlike, and indeed no way suggestive of, compositions and dosage forms comprising a drug and a medium chain fatty acid salt as the sole enhancer, as recited in applicants' claims.

Moreover, insofar as Watts demonstrates the inferiority of the insulin/capric acid mixture of the comparative example as compared to mixtures utilizing a two-component absorption enhancer, Watts teaches away from using a medium chain fatty acid or salt as the sole enhancer. Further, all of the compositions of Watts which include a medium chain fatty acid are disclosed in the form of a suspension in liquid form or cooled to a semi-solid. There is no teaching or suggestion to provide such compositions in any other form, and in particular, in a compressible form.

While one might nonetheless conclude from the teachings of Watts that medium chain fatty acids and their corresponding salts are interchangeable insofar as either may be used, it is critical to bear in mind that such suggested "interchangeability" must be viewed ***within the context of*** the dual-component microemulsions in which the medium chain fatty acid or its salt is combined with a surfactant, such as Labrasol. As a result, while the microemulsion context may create the ***appearance*** of interchangeability of medium chain fatty acids and their corresponding salts, when viewed outside of this context, such as in a context concerning compressible blends of a drug and an enhancer in particulate form, this interchangeability cannot be presumed to follow and is not provided by the teachings of Watts. From the physical data describing these two materials summarized in the table above, it is evident that there is no basis to consider these materials to be interchangeable in the context of a compressible blend of a drug and an enhancer.

In asserting Watts as an anticipatory reference, the Examiner has also relied upon the following passage appearing in the background section of Watts which states as follows:

> It has been known for some time that sodium caprate can act as an absorption promoting agent, probably by the perturbation of membranes or modification of tight junctions between cells (Kajii et al., J. Pharm. Sci. 77 390, 1988).

Watts at col. 2, lines 8-11. Yet an examination of this passage reveals that it contains nothing more than a passing reference to a generalized idea without reference to, among other things, the types of drugs for which absorption promotion is at issue, the types of dosage forms under consideration, or the contemplated routes of administration. Without anything further, and there is nothing further, this passage is the antithesis of the kind of precise and detailed disclosure that is required by the anticipation standards set by the Federal Circuit. Moreover, when taken in combination with the rest of the teachings of Watts, i.e., the use of a medium chain fatty acid or its salt in combination with a surfactant (e.g., Labrasol) to form a microemulsion, it is evident that Watts neither teaches nor suggests a compressible composition or a solid oral dosage form containing an absorption enhancer in which the absorption enhancer is:

1. in particulate form;
2. in a compressible blend admixed with a drug in particulate form;
3. a sodium salt of a medium chain fatty acid; and
4. a single-component enhancer – i.e., not combined with a dispersing agent such as Labrasol.

In the absence of such teachings, Watts fails to disclose the claimed invention with sufficient precision and detail as to establish that the subject matter existed in the prior art. Watts does not meet the disclosure standards required for anticipation and, therefore, cannot serve as the basis for a rejection under 35 U.S.C. § 102(b). Accordingly, the applicants request respectfully that the rejections based on Watts be withdrawn.

The Obviousness Rejection

Claims 178, 182-184, 186, 188, 198, 202-206, 209, 211-214, 222-224, 226, 228, 238-240, 244-246, 250, 251, and 253-256 stand rejected under 35 U.S.C. § 103(a) as being obvious over Watts in view U.S. Patent No. 6,017,559 to Mulqueen ("Mulqueen"). This rejection is respectfully traversed.

Applicants note that, as in prior Office Actions, Mulqueen is cited only with respect to certain of the dependent claims (now 205 and 206) for its purported disclosure of "two or more populations of particles." See Office Action at 7. Apart from the fact that Mulqueen fails to cure the basic deficiencies of Watts as an anticipatory disclosure with respect to the independent claims, and that Mulqueen is not directed to the pharmaceutical arts but rather to aqueous emulsions for use as pesticides and pigments, the claims cited by the Examiner with respect to Mulqueen have been amended so that the term "multiparticulate" no longer appears. As a result, the rejection of claims 205 and 206 based on Watts in view of Mulqueen has now been rendered moot.

Rejections under 35 U.S.C. § 112

Claims 178, 182, 184, 186, 188, 198, 202-206, 209, 211-214, 222-224, 226, 228, 238, 240, 244-246, 250, 251, and 253-256 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner considers the use of the transitional phrase "consisting essentially of" to be improper in view of the specification, and the phrase "enhancer combination." This rejection is respectfully traversed.

Without acceding to the correctness of the Examiner's position, the applicants note that the claims now pending, as set forth in the accompanying Listing of Claims, no longer employ the "consisting essentially of" transitional language, As a result, the Examiner's rejection based on the use of "consisting essentially of" has been rendered moot.

Conclusion

In view of the foregoing amendments and remarks, as well as the Declaration of James Swarbrick, D.Sc., Ph.D., the applicants respectfully submit that the case in condition for allowance. Accordingly, the applicants request respectfully favorable consideration and early issuance of a Notice of Allowance. If the Examiner believes any issues remain, or if minor amendments would address any such issues, the undersigned invites the Examiner to contact the undersigned for a telephone interview prior to the issuance of an Action.

Respectfully submitted,

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